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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,931	09/22/2003	Poh K. Hui	DM-6919 CNT(BMS-2441)	1625

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EXAMINER	
HUYNH, CARLIC K	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,931	HUI ET AL.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45 and 47-86* is/are pending in the application.

4a) Of the above claim(s) *85 and 86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45 and 47-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of applicants' amendments and remarks filed on July 11, 2007 is acknowledged.

Status of the Claims

1. Claims 45-86 are pending in the application in response to the Non-Final Rejection submitted on February 15, 2007. Applicants have cancelled claim 46 in an Amendment- After Non-Final Rejection filed on July 11, 2007.

Claims 85-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on November 20, 2006.

Accordingly, claims 45 and 47-84 are being examined on the merits herein.

Response to Arguments

2. Applicant's arguments, see "Remarks" filed on July 11, 2007, with respect to "Amendments to claim 53" for claim objection to claim 53 for being improper claim dependency has been fully considered and are found persuasive. Applicants have amended claim 53 to be dependent on claim 45. Thus, the Claim Objection has been withdrawn in light of the amendments.

3. Applicant's arguments, see "Remarks" filed on July 11, 2007, with respect to "typographical errors" to the specification has been fully considered and are persuasive. The specification has been amended to reflect the proper spelling of "acid" on page 4, 7, 8, 10, and 23

and "solvent" on page 13. Thus, the Objection to the Specification has been withdrawn in light of the amendments.

4. Applicant's arguments, see "Remarks" filed on July 11, 2007, with respect to "Rejections under 35 U.S.C. § 102(e)" to claims 45-46, 48, 50, and 52 has been fully considered and are found persuasive in part. The Applicants have argued that Nyberg et al. only teach extraction of sphingomyelin from a mixture of lipid not the preparation of a phospholipid blend of the instant invention.

Although it is true Nyberg et al. teach extraction of sphingomyelin from a phospholipid blend, Nyberg et al. nonetheless teach the phospholipid blend and its preparation. Thus, the Rejections under 35 U.S.C. § 102(e) to claims 45-46, 48, 50, and 52 remain.

5. Applicant's arguments, see "Remarks" filed on July 11, 2007, with respect to "Rejections under 35 U.S.C. § 103" to claims 45, 47, 49, 51, and 53-58 has been fully considered and are not found persuasive in part. The Applicants have argued that Nyberg et al. only teach extraction of sphingomyelin from a mixture of lipid not the preparation of a phospholipids blend of the instant invention.

Although it is true Nyberg et al. teach extraction of sphingomyelin from a phospholipid blend, Nyberg et al. nonetheless teach the phospholipid blend and its preparation. Thus, the Rejections under 35 U.S.C. § 103 to claims 45, 47, 49, 51, and 53-58 remain.

6. Applicant's arguments with respect to claims 45-84 have been considered but are moot in view of the new ground(s) of rejection. The following new ground(s) of rejection to amended claims 45 and 47-84 are used herewith.

Specification

7. The use of the trademark Filamatic® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 45, 48, 50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Nyberg et al. (US 5,677,472).

Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and

sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol) and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13^{O}-25^{O} C, and drying the precipitate (see example 1, 2, 6, and claim 1). Nyberg et al. specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2).

Regarding claim 50, Nyberg et al. teach warming the non-aqueous solvent system to 25^{O} C, which meets the limitations of the instant claim (example 1).

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 102(e).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 45 and 47-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg et al. (US 5,667,472) as applied to claims 45, 48, 50, and 52 above, in view of Fisher et al. (US 5,840,661), Unger et al. (US 5,585,112), and Unger (US 6,416,740), and as evidenced by Senior et al. ((Biochimica et Biophysica Acta, 1991, 1062, pp. 77-82).

The teachings of Nyberg et al. are discussed above.

Nyberg et al. explicitly indicate similar methods of extracting a phospholipid utilizing suitable solvent systems (column 3, lines 6-15). Nyberg et al. further teach the precipitation of a phospholipid mixture, "brown phase," by using suitable solvent systems (examples 2-3; specifically column 9, lines 54-57). Nyberg et al. also acknowledge the wide use of phospholipids in medical field (column 1, lines 17-30).

Nyberg et al. do not employ methyl t-butyl ether as an intermediate solvent and further fails to prepare phospholipid suspensions.

The teachings of Fisher et al. is solely used to show that methyl t-butyl ether and acetone are art equivalent solvents (column 59, lines 55-60).

Unger et al. teach suitable mixtures of phospholipids including dipalmitoylglycerophosphatidylcholine, dipalmitoylglycero phosphatidic acid, and phosphatidylethanolamine-PEG 5000 in combination with a gaseous perfluorobutane. Unger et al. further use polyols, such as polyethylene glycols, in preparing phospholipid suspensions (abstract; columns 2, 10, 12, 22, 25; and examples 1-3).

Unger teaches a method for sterilizing phospholipids suspensions (column 52, lines 47-56).

As evidenced by Senior et al., Senior et al. disclose dipalmitoylphosphotidylethanolamine (DPPE) covalently may be coupled to methoxypolyethylene glycol (MPEG 5000) (abstract). Senior et al. further disclose poly(ethylene glycol) (PEG) and MPEG 5000 are known in the art as equivalent substances to alter the surface properties of liposomes (page 78).

Accordingly, absence the showing of unexpected results, it would have been obvious to one of ordinary skill in the art to substitute the acetone of Nyberg et al. with methyl t-butyl ether, because as shown by Fisher et al., such organic solvents are art equivalents.

Further, absence the showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the phospholipid blend of Nyberg et al., as modified by Fisher et al., in polyols such as polyethylene glycol as taught by Unger et al., and formulate suitable phospholipid suspensions for therapeutic use, because such suspensions, as recognized by Nyberg et al. and taught by Unger et al., are readily used in the arts of drug delivery and ultrasonic imaging applications.

The motivation to combine the acetone as taught by Nyberg et al. with the methyl t-butyl ether as taught by Fischer et al. is acetone and methyl t-butyl ether are art equivalent organic solvents.

The motivation to combine the phospholipid blend of Nyberg et al. with the phospholipid blend of Fischer et al., Unger et al., and Unger is they are suitable phospholipid suspensions for use in medical imaging such as ultrasonic imaging applications.

Regarding claims 56-57, Unger et al. teach providing a dispersed phospholipids blend solution at $50^{O}C$, which meets the limitations of the instant claims (example 4A).

Regarding claims 58-59, Unger et al. teach the ratio of solid phospholipids blend to polyol solvent is 5 mg/mL, which meets the limitations of the instant claims (example 1). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the ratio of solid phospholipids blend to polyol solvent provided in a composition, according to the guidance set forth in Unger et al., to provide a

composition having the desired ratio of solid phospholipids blend to polyol solvent. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 68-70, Unger teach lipid aggregates are 200 nm in size and may be as small as 5-10 nm in size, which meets the limitations of the instant claims (column 26, lines 22-23).

Regarding claims 71-72, Nyberg et al. teach heating the aqueous solution to 40^{O}C (example 5). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the aqueous solution temperature provided in a composition, according to the guidance set forth in Nyberg et al., to provide a composition having the desired aqueous solution temperature. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 73-74, Unger et al. teach the phase transition temperature is 41^{O}C and the lipid solution temperature is 42-50^{O}C, which meets the limitations of the instant claims (example 8). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the lipid solution temperature provided in a composition, according to the guidance set forth in Unger et al., to provide a composition having the desired lipid solution temperature. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or

workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 75-78, Unger teaches filtering a phospholipid suspension through a sterilizing filter (column 52, lines 38-41), filtering using at least 1 filter (column 52, lines 4 and 17-19), the temperature of the filter (column 52, lines 57-59), and the filter pore size of 0.1-5 μm (column 52, lines 38-39), which meet the limitations of the instant claims.

Regarding claims 79-82, Unger teaches dispensing the phospholipid suspension into a vial (column 52, lines 26-29), a perfluorocarbon gas (column 28, line 21), perfluoropropane (column 28, line 26), and the method to exchange gas (column 29, lines 15-16), which meet the limitations of the instant claims.

Regarding claims 83-84, Unger teaches a method of sterilization (column 52, lines 26-29 and 47-56).

10. Claims 45 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US 6,521,211).

Unger et al. teach a process for preparing phospholipids comprising DPPA, DPPE-PEG5000, and DPPC (column 135, lines 29-31). The phospholipid mixture is added to a non-aqueous solvent system of methanol and toluene (column 135, line 34). The mixture was warmed to 55^{O}C and allowed to form a thick gel (column 135, lines 36 and 39). Methyl t-butyl ether was added to the mixture to precipitate the solid material at 25^{O}C and placed in a vacuum oven to dry (column 135, lines 40-42 and 44).

It is noted that Unger et al. teach preparing phospholipids comprising DPPA, DPPE-PEG5000, and DPPC minus the weight of DPGS-PEG-KQAGDV (column 135, 29-30). It

would be obvious to one skilled in the art that the phospholipids of Unger et al. contain DPPA, DPPE-PEG5000, and DPPC.

Conclusion

11. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

SHENGJUN WANG
PRIMARY EXAMINER